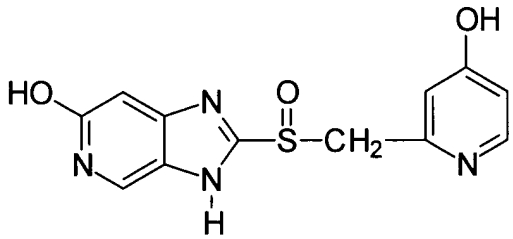
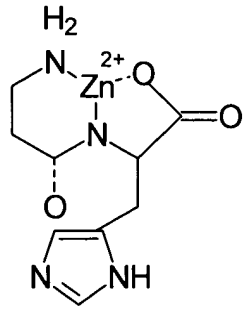
or of general formula II or III,



II



III

and

- at least one pharmaceutically acceptable excipient selected from the group which includes: a binder, an alkaline reaction compound, surface-active agents, a filling material and disintegrating-swelling excipients;

b) drying the active layer formed during said spraying to form a charged nucleus in said fluid bed coater; and

c) coating the charged nucleus in the fluid bed coater by spraying a solution which contains an enteric coating polymer with at least one pharmaceutically acceptable excipient selected from the group comprising: a plasticizer, a surface-active agent, a pigment and a lubricant, to form an gastro-resistant external coating layer.

REMARKS

New claim 36 has been introduced into the application. Claims 1 and 34 have been amended to recite that the layer containing the active ingredient formed on the inert nucleus is substantially non-porous. The claim amendments are supported by the disclosure in the originally

filed specification. By way of example, the Examiner's attention is invited to the specification at the bottom of page 8, as well as pages 10 and 16 and the application examples.

In Page No. 16, the Examiner rejected claims 1 to 13 and 15 to 34 under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,132,771 to Depui et al. ("Depui"). Additionally, claims 1 to 13 and 15 to 35 were rejected under 35 U.S.C. §103(a) as unpatentable over Depui. It is submitted these rejections are improper and should be withdrawn.

For a reference to anticipate a claimed invention, that single reference must show each and every feature of the claimed invention arranged as in the claim. See *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193 (Fed. Cir. 1993). That reference must contain sufficient disclosure as to convince one of ordinary skill in the art that the inventor had possession of the invention at the time the reference was filed. When a composition is claimed, an anticipating reference must completely identify the claimed composition, as it is set forth in the claim, and must also provide an enabling disclosure so that one of ordinary skill in the art can, without undue experimentation, make the invention. See In re Sheppard 144 U.S.P.Q. 42 (CCPA 1964). If a reference fails to properly identity the invention or to enable one to make the invention without undue experimentation, that reference does not describe the invention and cannot be an anticipatory reference.

It is submitted that the Depui reference does not anticipate the now claimed invention. It neither identifies the claimed invention, nor does it enable one of ordinary skill in the art to make the invention without undue experimentation.

The Depui patent, assigned to Astra-Zeneca, is directed to an oral pharmaceutical dosage form for a combined therapy against GORD (Gastro Oesophageal Reflux Disease). The dosage

form is preferably a tablet containing an acid suppressing agent (proton pump inhibitors i.e. omeprazol, lansoprazol,...) and a prokinetic agent (i.e. cisapride, mosapride,...).

The main objective of Depui is to provide an oral dosage form simultaneously containing both an acid suppressive agent and a prokinetic agent, but not enteric coating layered preparations of proton pump inhibitors.

In column 2, starting at line 47, Depui describes as obvious that the proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer and specifically refers to U.S. Patent No. 4,786,505 ("the 505 patent") for omeprazole preparations (see col. 2, lines 50-57) with a description of enteric coating layered preparations of proton pump inhibitors. The '505 patent is currently being asserted by one or more companies related to Astra-Zeneca against numerous generic companies seeking to market generic omeprazole pharmaceutical preparations.

The '505 patent discloses omeprazole pellets having a core containing omeprazole and an alkaline substance, one or more separating layers, and an outer enteric coating. The separating layer(s) are described as necessary because: *"The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discoloration of omeprazole during the coating process or during storage."(*see '505 col. 3, lines 4-8). U.S. Patent No. 4,853,230 (the '230 patent), also being asserted by affiliates of Astra-Zeneca, contains similar disclosure relating to other proton pump inhibitors (see col. 8, line 67 to col. 9, line 4).

Both the '505 (col. 3, lines 36 to 65) and the '230 (col. 8, lines 31 to 61) patents refer to the importance of the presence of an alkaline substance and both contain extensive disclosure as to

the necessity of the separating layer because of the acid sensitivity of omeprazole and the negative experiences in bio-studies of compositions without the separating layer.

Judge Jones, in her recent decision upholding the validity of both the '505 and the '230 patents, credited the testimony of the inventors which, *inter alia*, outline the problems that were encountered in dealing with the omeprazole compound and producing a suitable dosage form for its administration. The Court outlined years of work undertaken by the inventors and the company for which they work and indicated that ultimately the inventors decided to use a subcoating between the omeprazole containing core or the enteric coating and that further development work was required even if after they had come to this approach. The use of the separating layer was required because throughout their prior experimentation, they could not solve the problem of simultaneously maintaining the stability of the omeprazole and also providing a formulation with suitable shelf life, one that did not discolor and one that maintained its gastric acid resistance so that the active ingredient would be delivered at the proper target location in the body.

Depui fails to describe how a stable and useful oral form of a proton pump inhibitor can be made without having an alkaline reacting substance and at least one separating layer. That is to say, assuming that Depui ever contained sufficient disclosure to identify such a composition, it fails to contain enabling disclosure as to how to make such a composition.

All 14 examples described by Depui refer to a proton pump inhibitor dosage form having alkaline substance and at least one separating layer between the core and the surrounding enteric coating. The alkaline substance can be included as a basic salt of the corresponding proton pump inhibitor, i.e. omeprazole magnesium salt, as stated in the '505 (col. 4, lines 23 to 27) and '230

(col. 8, lines 55 to 61) patents. There is not a single example, suggestion or description of how to produce a stable and useful composition as defined in the presently pending claims.

The Examiner has referred to text regarding the enteric coating layer of proton pump inhibitors as "optional" for both the presence of alkaline reacting substances and separating layers(s). However, that disclosure is made generically and it is not supported by the cited prior art or by the patent description. Since the main object of Depui is a combined therapy for GORD, Depui sought broad protection and attempted to foreclose others from patenting a composition with no separating layer by a uninformative comment as to this possibility. However, Depui fails to describe how such useful and stable enteric coating layered forms without separating layer(s) can be made.

It is submitted that referring to an embodiment as "optional" does not translate into a disclosure or description of embodiments failing to employ the "option". This is especially true where, as here, the specification contains no written description of such an embodiment, no enabling disclosure of how to make or use the "optional" embodiments and, not only fails to provide a best mode, but fails to disclose any mode.

A mere mention of a possible embodiment is not so definite or particular that, without undue experimentation, one of ordinary skill in the art can gain possession of the claimed subject matter. See, Sheppard, supra. at page 45. Characterizing a feature as "optional" does not convey to one of ordinary skill in the art that the inventor had possession of that option or all other options. Accordingly, the Depui disclosure is not enabling to prepare stable and useful proton pump inhibitor oral dosage forms without having at least a separating layer. Hence there can be no anticipation.

Depui is not the only document to generically mention two-layered granules containing anti-ulcer benzimidazole compounds.

The PCT International Search Report (ISR) for WO 99/06032 cited example 6 of EP 642797 ("Takeda") as the closest prior art. That reference was submitted to the Examiner herein with the filing of the application.

Takeda relates to pharmaceutical compositions containing two different active compounds:

- an antibacterial substance (not related to benzimidazole anti-ulcer compounds), and

- an anti-ulcer substance of the same kind as described in the patent application, being the pharmaceutical composition a gastrointestinal mucosa-adherent solid preparation.

The antibacterial substance is an antibiotic, e.g. amoxicillin, against *Helicobacter pylori* (HP), a bacteria which promote gastric ulcers. The anti-ulcer substance, e.g. lansoprazole, acts on the eventually formed ulcers.

According to Takeda, the pharmaceutical compositions must be adherent to the gastric mucosa, causing it to remain for a longer period in the gastrointestinal tract and hence to improve the bioavailability of active ingredients. To obtain this result Takeda teaches mixing any of two active substances, or previous oral forms containing them, with material showing adherence to the gastric mucosa. The only reference in Takeda to multi-layered granules containing anti-ulcer benzimidazole compounds is example 6 of pages 16 and 17, which literally reads as follows:

Example 6

Production of a formulation comprising lansoprazole and a gastrointestinal mucosa-adherent solid prepration containing AMOX

1) Granules containing lansoprazole was prepared as follows:

Ingredients	mg
Lansoprazole	30
Magnesium Carbonate USP	22.4
Sugar Spheres NF	110.0
Sucrose NF	59.8
Starch NF	36.4
Low-Substituted Hydroxypropyl Cellulose NF (L-HPC-31)	40.0
Hydroxypropyl Cellulose NF (HPC-L)	1.4
Methacrylic Acid Copolymer LD (Eudragit L30D-55) (Röhm Pharma Co.)	44.6
Polyethylene Glycol NF (PEG-6000)	4.4
Titanium Dioxide USP	4.4
Polysorbate 80 NF (Rheodol TW-0120)	2.0
Talc USP	14.0
Colloidal Silicon Dioxide NF (Aerosil)	0.6
Purified water* USP	q.s.
Total	370.0
*: Removed during the manufacturing process USP; The United States Pharmacopeia NF: The National Formulary	

Sugar spheres was coated with a mixture of lansoprazole, magnesium carbonate, sucrose, starch and L-HPC-31 by means of spraying aqueous HPC-L solution in a centrigual fluid-bed granulator (CF-1000S, Freund Co.) and the resultant wet granules were dried in a vacuum oven at about 40°C for about 18 hours, and then sieved. The obtained granules were coated with aqueous enteric Eudragit suspension containing PEG-6000, talc, titanium dioxide and Rheodol TW-0120 in a fluid-bed coater (F10-Coater FLO-80, Freund Co.), and sieved, and then dried in a vacuum oven at about 42°C for about 18 hours. The obtained granules were mixed with talc and Aerosil.

2) 370 mg of granules containing lansoprazole as obtained in 1) above and 100 mg of gastrointestinal mucosa-adherent solid preparation containing AMOX as obtained in Reference Example 3 were packed in No. 0 capsules to yield a capsule preparation.

Both the PCT ISR and IPER, specifically pointed to example 6 of the Takeda patent.

Accordingly, the above example 6, obviously its point 1, was considered as the closest prior art to the patent application, because it was the only prior description of two-layered

granules (an inert core and two layers) containing anti-ulcer benzimidazole compounds (lansoprazole).

Following the IPER, an experimental protocol was undertaken trying to reproduce the lansoprazole granules supposedly described in the example 6 of the Takeda's patent.

Attached hereto is a Declaration by Dr. Molina, Mr. Picornell and Mr. Bravo, three pharmaceutical technology experts. Mr. Picornell is also the inventor of the patent application. Set forth in the Declaration are the attempts to reproduce example 6 of Takeda. The declarants even attempted to correct the defects of the procedure of example 6. The experimental work done by the above-mentioned declarants led to the following conclusion:

> *"Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastrointestinal granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO/06032, particularly as described in example 1 therein."*

The now claimed oral pharmaceutical preparations are two-layered granules substantially spherical, with a homogenous active charge layer and a substantially non-porous surface, and they are acid-resistant but dissolve rapidly in alkaline medium.

The attached Declaration shows that such two-layered granules are not obtainable by the procedure described in example 6 of Takeda, even introducing amendments to correct the defects of the example 6 procedure.

As can be seen, the preparation of compositions of the type now claimed is not a trivial matter. Depui's cavalier attitude in failing to include a description or example of how to produce

a dosage form without a separating layer should not be considered as an enabling disclosure. Takeda provides substantially more detail for the example 6 procedure than the passing mention of Depui of an embodiment with no separating layer. Accordingly, there is no basis in the record to consider Depui as enabling of the now claimed invention.

Starting on page 3 of the Official Action, the Examiner comments on the previously submitted remarks. Applicant will now address the Examiner's remarks regarding Applicant's previously submitted remarks.

Applicants have referred the Examiner to the decision in the omeprazole litigation which contains a comprehensive explanation of the problems that were solved by the separating layer. While the Examiner is correct that simply because the '505 reference teaches the benefits of a separating layer it does not prohibit Depui from teaching a composition without a separating layer, Depui must actually describe (identify and enable) the now claimed invention without a separating layer. This is not achieved by using the word "optional".

Applicants recognize that they are proceeding in manner contrary to the prior art. This is exactly one of the reasons why the now claimed composition is patentable over the prior art. The Examiner's comment that Applicants' instant specification fails to give specific guidelines to make the formulation is in error. See pages 8, 10 and 16 of the specification as originally filed and the specification examples. None of Depui's 14 examples produce a formulation without a separating layer. Thus, the Examiner's criticism of Applicants' argument is unjustified.

While it is true that a patent is not limited to its examples, a patent is also not interpreted to cover or describe that which it does not adequately disclose in accordance with 35 U.S.C. 112. Use of terms such as "may" or "optional" does not convert a non-described embodiment to a described embodiment. At best, Depui discloses wishful thinking with respect to formulations

that do not employ a separating layer but this does not constitute sufficient written disclosure or enablement or suggestion to one of ordinary skill in the art.

Whether claim 1 of the Depui reference would be construed to cover an embodiment without a separating layer is not what is at issue here. Claim construction is a question of law resolved after extensive discovery, briefing, argument and generally a detailed study of the prosecution history. In some instances there is a need to resort to extrinsic evidence such as expert testimony. At the very least, claim construction involves a review of the entirety of the specification and prosecution history. Therefore, the Examiner's rebuttal that claim 1 "teaches" a formulation comprising coats covered with an enteric coating layer is in error. The claims of Depui teach nothing with respect to the particular embodiment now claimed.

Claims 1 and 35 have been rejected under 35 U.S.C. §103 as unpatentable over Depui in view Lovgren et al., EP 0 244 380 B1. It is submitted the rejection is improper and should be withdrawn.

The Lovgren reference teaches the necessity of the separating layer. Therefore, to combine this reference with Depui is improper since a vital and important part of the Lovgren reference would have to be disregarded. Clearly, the Examiner is engaging in a pick and choose technique to formulate an obviousness rejection based on hindsight reconstruction. This is improper under 35 U.S.C. §103. Also see In re Ratti 123 U.S.P.Q. 349 (CCPA, 1959).

In view of the foregoing, reconsideration and allowance of the application with claims 1 to 13 and 15 to 36 are earnestly solicited

A check in the amount of $9.00 is enclosed in payment for the addition of 1 dependent claim.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

By _____

Vincent M. Fazzari, Reg. No. 26,879
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

Dated: November 18, 2002

AMENDMENTS TO THE CLAIMS SHOWING CHANGES

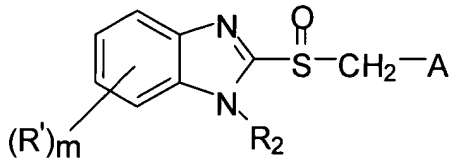
IN THE CLAIMS:

1. (Three times amended) An oral pharmaceutical preparation consisting essentially of:

a) an inert nucleus;

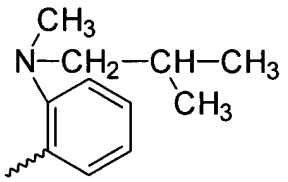
b) a substantially non-porous soluble active layer or layer which disintegrates rapidly in water, made from a single aqueous or hydroalcoholic solution-suspension which comprises:

- an active ingredient of anti-ulcer activity of general formula I



wherein:

A is:



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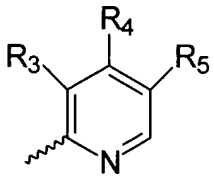


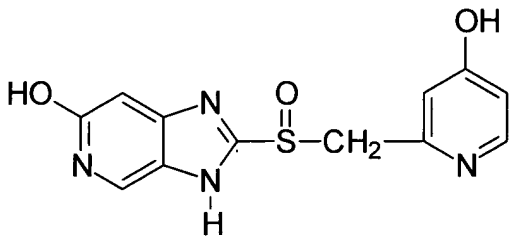
in which: R^3 and R^5 are the same or different, and may be hydrogen, alkyl, alkoxy, or alkoxyalkoxy;

R^4 is hydrogen, alkyl, alkoxy which can optionally be fluorated, alkoxyalkoxy, or alkoxycycloalkyl;

R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulphinyl;

R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonilmethyl, alkoxycarbonilmethyl or alkylsulfonil; and, m is a whole number from 0 to 4;

or of formula II or III,



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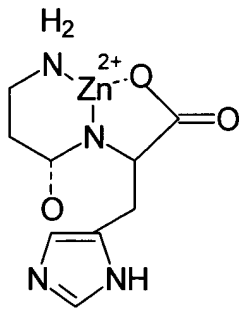


III

and

- at least one pharmaceutically acceptable excipient selected from the group which includes: a binder, an alkaline reaction compound, a surface-active agent, a filling material and a disintegrating-swelling excipient; and

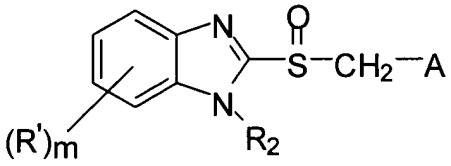
c) a gastro-resistant outer coating on the layer of (b), wherein said gastro-resistant outer coating is made from a solution which includes:

- an enteric coating polymer; and
- at least one excipient chosen from the group which includes: a plasticizer, a surface-active agent, a pigment and a lubricant.

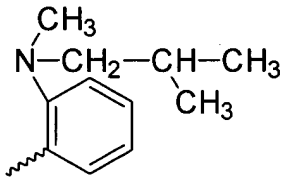
34. (Amended) A process for making an oral pharmaceutical preparation comprising:

a) coating an inert nucleus to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension-solution, which comprises:

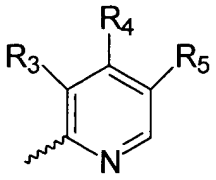
- an active ingredient of anti-ulcer activity of general formula I:



wherein A is:



or



wherein R^3 and R^5 are the same or different, and may be hydrogen, alkyl, alkoxy, or alkoxyalkoxy;

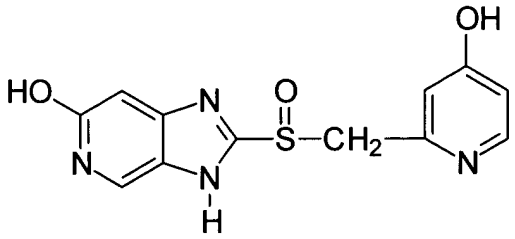
R^4 is hydrogen, alkyl, alkoxy which can be fluorated, alkoxyalkoxy, or optionally alkoxycycloalkyl;

R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulphinyl;

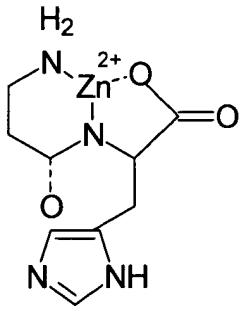
R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonilmethyl, alkoxycarbonilmethyl or alkylsulfonil; and, m is a whole

number from 0 a 4;

or of general formula II or III,



II



III

and

- at least one pharmaceutically acceptable excipient selected from the group which includes: a binder, an alkaline reaction compound, surface-active agents, a filling material and disintegrating-swelling excipients;

b) drying the active layer formed during said spraying to form a charged nucleus; and

c) coating the charged nucleus by spraying a solution which contains an enteric coating polymer with at least one pharmaceutically acceptable excipient selected from the group comprising: a plasticizer, a surface-active agent, a pigment and a lubricant, to form an gastro-resistant external coating layer.